

**35 U.S.C. § 103**

Claims 3, 4, and 7-14 have been rejected under 35 U.S.C. § 103 as allegedly being unpatentable over the Rowinsky et al., Holmes et al., and Gilman et al. references of record. The Examiner indicates that applicants' remarks in the amendment filed on September 12, 1994, and the Declaration of Wyndham H. Wilson filed October 7, 1994 have been noted. The Examiner further indicates that the declaration of Dr. Wilson "fails to show a comparison of applicants' 17.5-35 mg/m, [sic] per day for 96 hours vs. the Gilman et al. range of 30 mg/m, [sic] per day for 5 days". See. Office Action. 11/28/94. p.3. The Examiner also states that the Gilman et al. reference is "clearly the closest prior art". Id. p.3.

Applicants traverse the rejection.

In view of the Examiner's primary and stated reliance on the contents of the above-mentioned Gilman et al. reference as the "closest prior art", and in view of the discussion of the specific disclosure of this reference with the Examiner during the Examiner Interview on March 1, 1995 with Dr. Wilson and Mr. Haight, applicants have addressed herein the reasons that the Gilman et al. reference does not make obvious the invention as presently claimed.

Notwithstanding, it is respectfully maintained that the disclosures of the cited Rowinsky et al. and the Holmes et al. papers do not make obvious applicants' invention as claimed for the reasons previously detailed at length in the responsive amendment filed for this application on September 12, 1994 (see pages 4-6 of the 9/12/94 amendment), for the reasons set forth in the Declaration of Dr. Wyndham H. Wilson filed on October 7, 1994, and for the reasons provided in the responsive amendment filed on November 8, 1993 in the parent application, U.S. Serial No. 07/950,380 (see pages 4-11 of the 11/08/93 amendment).

In addition, to clarify the record, it is respectfully submitted that the Gilman et

al. reference of record is more correctly cited as the textbook, *The Pharmacological Basis of Therapeutics*, 1990, Eighth Edition, Eds., Alfred Goodman Gilman, M.D., Ph.D., Theodore W. Rall, Ph.D., D.Med (Hon.), Alan S. Nies, M.D., and Palmer Taylor, Ph.D., Pergamon Press, Inc., Maxwell House, Fairview Park, Elmsford, New York (also referred to as "Goodman and Gilman" or "the Goodman and Gilman textbook" herein).

With regard to the "30 mg/m<sup>2</sup> per day for 5 days" maximal dose of taxol stated in the Goodman and Gilman textbook, it is respectfully submitted that this dose as provided does not make obvious applicants' claimed taxol treatment schedule which requires that taxol be infused intravenously into a patient at a continuous dosage rate of between about 17.5 to 35 mg/m<sup>2</sup>/24 hours to infuse between 70 and 140 mg/m<sup>2</sup> of taxol over a period of 96 hours into said patient (as recited in new claim 15).

As discussed during the above-mentioned interview held with the Examiner, the Goodman and Gilman textbook is completely silent concerning the dosing schedule or regimen by which the stated maximal taxol doses are administered or provided to an individual. Thus, it is respectfully contended that those having skill in the art are not taught, and therefore have no way of knowing, how the maximal taxol doses stated in Goodman and Gilman are given to an individual. This fact is supported by the accompanying Declaration of Bruce Chabner ("the Chabner Declaration", attached hereto as Exhibit 1).

As explained in the Chabner Declaration, Dr. Chabner is co-author with Dr. Paul Calabresi of Chapter 52 of the Goodman and Gilman textbook in which the cited maximal taxol dose is presented. As one having knowledge and experience in the art, Dr. Chabner asserts that the statement in which maximal taxol doses are recited is ambiguous and is deficient in that it does not provide or designate the dosing schedule or regimen by which taxol is administered (See Chabner Declaration, ¶¶ 6, 7, 9 and 10); therefore, as concluded by Dr. Chabner, the taxol dosing schedule or regimen cannot be determined from the

Goodman and Gilman disclosure. Dr. Chabner also maintains that those skilled in the art do not make assumptions concerning the dosing schedule or regimen of a drug or pharmaceutical composition when the dosing schedule or regimen is not explicitly stated in a reference or publication. With particular regard to the taxol doses stated in the Goodman and Gilman textbook, Dr. Chabner also maintains that those skilled in the art would not assume that taxol is administered by continuous infusion, based on the lack of information provided authors P. Calabresi and B. Chabner in Chapter 52.

In sum, while the presently claimed invention requires intravenous infusion of the recited low doses of taxol into a patient at a continuous dosage rate over a 96 hour period of infusion time, there is no teaching in the Goodman and Gilman reference describing how taxol is administered to a patient. Indeed, the silence of the cited reference regarding the taxol dosing schedule or regimen leaves in question the taxol dosing schedule by which taxol is given, e.g., by discontinuous bolus; by discontinuous infusion; or by continuous infusion, in the 5 day time period stated in Goodman and Gilman. Thus, it is respectfully asserted that, for all practical purposes, Goodman and Gilman's statement reporting a maximal taxol dose is virtually not useful to the skilled artisan in the absence of an accompanying teaching of the dosing regimen or schedule to use.

Based on the foregoing discussion and remarks, in conjunction with the Chabner Declaration, it is respectfully submitted that the invention as presently claimed provides a novel discovery to the art and is unobvious and patentably distinct in view of the cited art. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 103 is respectfully requested.

**CONCLUSION**

For the reasons presented above, applicants respectfully believe that the subject matter of the claimed invention is patentably distinguished over the cited art and that the application and claim as presented are now in condition for allowance. An action passing this case to issue is courteously urged.

In the event that the Examiner is of the opinion that further discussion of the application would be helpful, the Examiner is respectfully requested to telephone applicants' undersigned representative at (212) 415-8751 and is assured of full cooperation in an effort to advance the prosecution of the instant application and claims to allowance.

Respectfully submitted,

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